CENTRAL SLEEP APNEA AND HEART FAILURE: PAP VERSUS OXYGEN VERSUS PHRENIC NERVE STIMULATION

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Lisa Wolfe, MD, is originally from Ohio and did her medical school training at the Ohio State University. Her residency/fellowship training was at Northwestern University where she has been ever since. She is an associate professor of both medicine and neurology – where she is on the faculty in pulmonary / sleep and neuromuscular medicine. She is also the medical director of respiratory care at the Shirley Ryan Ability Lab (previously known as the Rehabilitation Institute of Chicago (RIC)). Dr. Wolfe’s academic focus is on the use of home based ventilation and the care of those with neuromuscular diseases. She has clinical grants for this work from the Les Turner ALS Foundation and the Muscular Dystrophy Association.
Overview

- Central Sleep Apnea Definitions
- Therapies
  - Acute care : PAP-ST
  - Chronic care
    - Medical therapy
    - CPAP
    - ASV
    - PAP ST
    - Phrenic Pacing
    - Oxygen
- COI - None related to this talk
### Central Sleep Apnea Definitions

<table>
<thead>
<tr>
<th>Types of Definition</th>
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<td>• PSG – an event</td>
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**CSA is complicated because of the language**

- To understand therapy choices you need to better understand the constructs that define central sleep apnea and in the larger sense – understand control of breathing

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**Polysomnographic Central Apnea**

Sleep hypoventilation is scored when the CO2 is:
- $> 55$ mm Hg for $\geq 10$ mins.
- $\uparrow \geq 10$ (compared to awake supine) to $>50$ for $\geq 10$ mins.

Cheyne-Stokes breathing is scored when both of the following are met:
1. There are episodes of $\geq 3$ central apneas / hypopneas separated by a crescendo and decrescendo change in breathing
   A) a cycle length of at least 40 seconds (typically 45 to 90 seconds)
   and
2. $\geq 5$ central events /hr

Central Sleep Apnea Definitions

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A diagnosis of central sleep apnea (CSA) requires all of the following:
1. An apnea–hypopnea index ≥ 5
2. Sum total of central apneas plus central hypopneas > 50% of the total
3. CAHI* ≥ 5 per hour
   AND
4. Presence of either sleepiness, difficulty initiating or maintaining sleep, frequent awakenings, or non restorative sleep, awakening short of breath, snoring, or witnessed apneas
   AND
5. No evidence of daytime or nocturnal hypoventilation

1) K. Terzisky; A Draganova Advances in experimental medicine and biology, 2018, Vol.1067, p.327-351

CSA is a marker of poor prognosis in CHF
Survival for those with HFrEF and CSA (AHI 34/h) was 45 months vs. 90 months for those without CSA (AHI <5/h, P = 0.02)
### Central Sleep Apnea Definitions

#### Types of Definition
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#### Special Notes
- Not all types of HST are appropriate for the evaluation of CSA.
- CSA diagnosis, central apnea–central hypopnea index (CAHI) is defined as the average number of episodes of central apnea and central hypopnea per hour of sleep without the use of a PAP device.
  - 327.27/ G47.37
- For Complex Sleep Apnea/ (CECA), the CAHI is determined during the use of a PAP device after obstructive events have disappeared.
  - 327.21/ G47.31
- E0470 – Spontaneous Bi-level PAP
- E0471 – Spontaneous Timed Bi-level PAP
- Note what is not approved in this scheme:
  - CPAP
  - Oxygen

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### Central Sleep Apnea Definitions

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#### Age – Controversy
- Some data has demonstrated no role for age (Bitter)
- My experience is that older patients are at greater risk (Javaheri)

#### Gender- men are at higher risk
- CO2 Gap
- Weight
- Hormonal Factors
- Autonomics
- Genetic

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Bitter Sleep 2012 Sleep Breath 16(3):781–79
Central Sleep Apnea Definitions

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In CHF
1) Resting CO2 is to low
2) Pt’s over ventilate

- Age
- Gender
- CO2 Gap
- Weight
- Hormonal Factors
- Genetic
- Autonomics

2) Madalina Macrea, Eliot S. Katz and Atul Malhotra Principles and Practice of Sleep Medicine, Chapter 109, 1049-1058.e5
Central Sleep Apnea Definitions

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LEPTIN

1) OSA -- Leptin resistance – and associated ELEVATED Leptin levels is known to be associated with OSA
2) CSA -- in CHF patients is associated with LOW leptin levels:
   1) A cut-off value for leptin concentration < 5 ng mL has a sensitivity of 50% and specificity of 89%.
3) CHF patients had no issues with obesity

2) Berger et al AJRCCM Articles in Press. 2018

Genetics

1) Population based genetics – in China HSPB7 gene
2) Specifics of genetic models with central apnea and heart disease:
   • Phox 2 B gene –
     • Associated with CCHS
     • NREM hypoventilation
     • Systole and sudden death
     • Mechanism - autonomic dysfunction
   • Mitochondrial –
     • Associated with many (PLOG/ Kearn-Sayers/ Leights/etc):
       • central apnea separate from myopathy
       • Risk for myopathy, heart block
       • Mechanism – Failure of oxygen sensing
3) Genetic models with heart disease but NO central sleep apnea
   • Duchene Muscular Dystrophy ( all dystrophin mutations)
   • Myotonic Dystrophy

Central Sleep Apnea Definitions

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Atrial Fibrillation

1) The prevalence of Atrial Fibrillation is high in those with heart failure and CSA
   - OR = 4.13; 95% CI 1.53 to 11.14

2) The prevalence of Atrial Fibrillation in CSA overall is high but not as high as in those with CHF
   - OR = 1.83, 95% CI: 1.69–2.00, p < 0.0001

- Age
- Gender
- CO2 Gap
- Hormonal Factors/Weight
- Genetic
- Autonomics

1) Ratz et al - SLEEPJ, 2018, 1–10
Central Sleep Apnea Definitions

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   - Which came first the chicken or the egg?

1) Ratz et al - SLEEPJ, 2018, 1–10

Central Sleep Apnea Therapies

**Therapy**

- Choices should be divided into needs for Acute Care vs Chronic Care
- First option is always to optimize CHF care
- Next option is PAP therapy
  - CPAP
  - Bi-Level
  - Servo- Ventilation
- Another option is low flow oxygen therapy
- Last option Phrenic Nerve Pacing

Central Sleep Apnea Therapies – The Modes

Patient driven effort to breath

ASV

Negative feedback control in which a measurement (MV - ResMed or PIF - Respironics) is compared with a target value and the difference is used to vary IPAP on a breath-by-breath basis.

Central Sleep Apnea Therapies – Acute Care

- The high WOB due to excess interstitial and alveoli fluid results in a risk of respiratory failure
- PAP reduces WOB but also may reduce CO
- The use of PAP therapy improves ICU outcomes in AD-CHF as compared to intubation
- There is a large variation in practice hospital to hospital which negatively impacts outcomes


- CPAP and NIV compared to O2 :
  - Reduce dyspnea, WOB, LOS in ICU and need for intubation.
- CPAP may be preferred
  - Cheaper
  - Easier to use
  - Can be started in the field
- NIV may be preferred in the ICU because of a better reduction in need for intubation
  - Has been shown to reduce autonomic load
  - Endorsed as best choice by the European Society of Cardiology
Central Sleep Apnea Therapies – Acute Care

**Acute Care – Titration Recommendations**

- **Start with low levels of PEEP (3–4 cmH2O) and pressure support of 7–8 cmH2O**
- **Increasing it progressively targeting tidal volumes are 4–7 mL/kg**.
  - PS of 10–18 cmH2O and PEEP of 4–7 cmH2O (IPAP 14–25 cmH2O/EPAP 4–7 cmH2O)
- **High pressures may cause:**
  - Excessive air leakage
  - Asynchrony
  - Discomfort
  - Aerophagia/aspiration
  - Hypotension due to falling CO


Central Sleep Apnea Therapies- Chronic Care

**Standard of Care for HFrEF**

- ↑BNP/PCWP/ or PAP is associated with and increase risk in CAHI
- First step is always optimizing CHF therapy
- **Afterload reduction** helps
  - Carvedilol – ↓BNP/↑LVEF
  - ↓total AHI at 6 mo (34 to 14)
  - ↓CAI (13 to 1.9)
- **Cardiac resynchronization therapy**
  - If atrial over drive pacing improves CO/EF – THEN the CAI ↓ (34 to 28)
  - Highly variable results
- **Case reports** – Transplant and LVAD resolves CSA
- **Positional therapy** – non supine position reduces CSA
  - Non cardiac mechanism

2) Vazir et al International Journal of Cardiology 2010 (138) 3, P 317-319
3) Oldenberg et al Sleep Medicine 10 (2009) 726–730
5) Traversi et al Sleep Medicine Volume 34, June 2017, Pages 30-32
Central Sleep Apnea Therapies – Chronic Care

OSA

• “Wine Bottle Hypothesis”
  • Rostral fluid shifts increase obstructive events in those with HFrEF
• Obstructive events: ↑LV afterload, ↑sympathetic tone, ↑BP

Prevalence of OSA in CHF

2) Khattak et al Tex Heart Inst J 2018;45(3):151-61

Central Sleep Apnea Therapies – Chronic Care

OSA

• Severe OSA (AHI >30) independently predicted 6-month cardiac hospital readmissions in patients with HFrEF. (Khayat)
• Other studies are hard because they mix OSA with CSA – But all show an increase in mortality especially for severe OSA patients with HFrEF.

CPAP – OSA and Mortality

1) Khattak et al Tex Heart Inst J 2018;45(3):151-61
2) Kasai et al CHEST 2008;133:690 – 696
Central Sleep Apnea Therapies – Chronic Care

**CSA in CHF with CPAP**

- Early *small* trials of CPAP in CSA with HFrEF
  - ↓ AHI
  - ↓ BNP
  - ↓ plasma catecholamine
  - ↑ LVEF
  - ↑ trend towards improved survival

**CANPAP**

1) Large trial ~100 in each grp
2) CPAP to treat CSA in HFrEF
3) When CPAP was able to resolve events the outcomes were good
4) If CSA persisted mortality was increased

**Was the CPAP success really treating central disease?**

1) Pearse et al European Journal of Heart Failure (2016) 18, 353–361
2) Artrz et al Circulation. 2007;115:3173-3180

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Central Sleep Apnea Therapies – Chronic Care

**Bi-level S and ST**

- There is no benefit of Bi-level (S) as compared to CPAP therapy
- There is no difference in responders and non responders
- There is a theoretic concern that the Bi-Level (S) could worsen CSR by dropping CO2

Khoinein et al Eur Respir J 2002; 20: 934–941
Central Sleep Apnea Therapies – Chronic Care

### Bi-level ST

- Arousals were reduced proportionally to the reduction in CAI
- ↑SWS and REM both Bi-levelST and ASV but not with oxygen or CPAP.
- Patients preferred ASV

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Central Sleep Apnea Therapies – Chronic Care

**What went right before the trial?**

- Why treat central apnea?
- Reversing the following have been shown to benefit cardiovascular outcomes:
  - Hypoxia
  - Arousals
  - Increased sympathetic activity

**What went right before the trial?**

- ASV improve hemodynamics at 6 mo:
  - ↓preload and ↓afterload
- Urinary metanephrines declined after 4 weeks on ASV
- ASV ↓ sympathetic nerve activity (SNA)
- ↑LVEF by echo after 6 months of ASV
- ↓NYHA class after 6 months of ASV
- ↑QOL (SF-36) at 3 mo of ASV vs CPAP

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Central Sleep Apnea Therapies – Chronic Care

**Servo Ventilation**

- **N= 1325**
  - HFrEF (9-71%), T-AHI ≥15, C-AHI ≥ 50%
- **Plan**
  - RCT = Std Care vs STD Care + ASV
  - Time to first event analysis
- **All-cause mortality ↑ with ASV**
  - hazard ratio 1.28  P=0.01
- **Cardiovascular mortality ↑ with ASV**
  - hazard ratio 1.34  P=0.006

**Primary End Point:**
- a) Death from any cause
- b) Lifesaving cardiovascular intervention (transplantation, LVAD, ROSC, or shock from AICD)
- c) ADHF with hospitalization

Cowie et al n engl j med 373;12

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**What went wrong?**

- **Was there insufficient compliance?-- NO**
  - 60% of ASV grp had use ≥ 3 hr/nt
  - Re analysis for compliance (on-treatment analysis) showed no difference in outcome
    - Hazard Ratio dropped from 1.37 to 1.28

- **Did the device fail?– NO**
  - At 12 months, the mean AHI was 6.6
  - Attempts to look statistically at AHI vs outcome made no difference in hazard risk

**What went wrong?**

- **Did ASV negatively impact the heart? --- NO**
  - No differences at up to 12 mo for:
    - Cardiac MRI
    - Echo
    - BNP– (down in both groups)
    - Inflammatory markers
      - troponin T, troponin I, sST2, galectin-3, cystatin C, creatinine, NGAL, hs-CRP and TNF-α

2) Cowie et al n engl j med 373;12
Central Sleep Apnea Therapies – Chronic Care

What went wrong?

- CSA might represent a compensatory mechanism with protective effects in HFrEF patients.
- The device algorithm changed during the course of the study.
  - The addition of autoEPAP
  - Allows PS = 0
  - Reduction in rate of increase ↑ in PS
  - Rapid ↓ PS when pressure support requirements remain stable

What went wrong?

- Alkalosis due to over ventilation may have increased risk of arrhythmia.
- Although the mean AHI and O2 stats were normal there were outliers.

1) Khayat et al CHEST 2016; 149(4):900-904

Pacing and Central Apnea

- Unilateral, transvenous phrenic nerve stimulation
- In CSA associated CHF the stimulation results in:
  - a more regular breathing pattern
  - fewer apneic events
  - improved oxygen saturation
  - increased end-tidal carbon dioxide
    - without suppressing the intrinsic drive to breathe

William T. Abraham
J Am Coll Cardiol HF
2015;3:360-9
Pacing and Central Apnea

6 month prospective trial

- N=57
- 55% reduction in apnea-hypopnea index from baseline to 3 months
  - But AHI remained in the abnormal range (44.9 to 22.4)
  - Persistent events are obstructive
- Improved
  - Sleep quality
  - Daytime sleepiness
  - Oxygenation
- Serious adverse events occurred in 26%
- Results unchanged at 6 months

William T. Abraham
J Am Coll Cardiol HF
2015;3:360–9

Reméde System Pivotal Trial

- Prospective RCT
  - N= ~75 in each grp
  - 31 sites(Europe & US)
  - PSG baseline and 6 mo
    - Baseline ave. AHI 46
    - Baseline ave. CAHI 28
  - 64% with HFrEF
  - 40% with Afib
- Primary outcome
  - ≥50% reduction in AHI

Reméde System Pivotal Trial Outcomes

- At 6 mo Paced pt’s statistically significant improvements
  - AHI 26
  - CAHI 6
  - ESS = - 3.6
  - Global Assessment = 55% improvement

Specifically in reference to your overall health, how do you feel today as compared to how you felt before having your device implanted?
1. Markedly worse
2. Moderately worse
3. Slightly worse
4. No change
5. Mildly improved
6. Moderately improved
7. Markedly improved

Maria Rosa Costanzo, Lancet 2016; 388: 974–82
Maria Rosa Costanzo, Lancet 2016; 388: 974–82

Pacing and Central Apnea
Remedé System Pivotal Trial Outcomes

AHI in Paced Pt’s

AHI in Control Pt’s

Central Sleep Apnea Therapies – Oxygen Therapy

Classic study of O2 for HCSR

- O2 response was variable
- The hypothesis was that severity of disease would predict response
- That was not the case

2) Javaheri et al SLEEP, Vol. 22, No. 8, 1999
Central Sleep Apnea Therapies – Oxygen Therapy

- Given the hyperpnea mechanism of CSR a mechanism to increase CO₂ may buffer the process
- Oxygen therapy has been shown to effectively reduce central sleep apnea
  - But there is a variable response
  - Base line CO₂ inversely predicts response to oxygen therapy

2) Javaheri et al SLEEP, Vol. 22, No. 8, 1999

There are responders and non responders to low flow O₂ therapy

Inverse relationship between CO₂ and response to NC-O₂. The cut off for a 50% response is 32

Central Sleep Apnea Therapies – Oxygen Therapy

Table 3. Multivariate regression analysis for the variables contributed to the variance of %dAHI.

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<th>P value</th>
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<tr>
<td>Age</td>
<td>0</td>
<td>0.63</td>
</tr>
<tr>
<td>BNP</td>
<td>0</td>
<td>0.76</td>
</tr>
<tr>
<td>P₄,CO₂</td>
<td>−26.3</td>
<td>0.004</td>
</tr>
<tr>
<td>AHÍ</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Ventilatory response to CO₂</td>
<td>0</td>
<td>0.74</td>
</tr>
<tr>
<td>Circulation time</td>
<td>0</td>
<td>0.89</td>
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- Control of heart failure does not explain the response to NC-O2

Should we be treating this anyway?

“Oxygen is a toxic gas”
MT Naughton ATS 2018

- IF CSA-HCSB continues despite the “optimal therapy,
  - THEN CSA-HCSB itself, is a compensatory mechanism to offset the adverse effects of HF
- CSA-HCSB offset the known adverse effects of HF
  - edematous lungs with restricted lung volumes
  - exhaustion due to an increased WOB
- The dyspnea of HF is akin to walking up a steep hill, and CSA-HCSB is akin to stopping periodically to “catch your breath.”
- Efficiency of breathing (pressure time product) in CSA-HCSB is improved
- CSA-HCSB can assist forward cardiac output.
  - The adrenaline surge augments stroke volume

Should we be treating this anyway?

Glottic closure at the end of a CSA event my help to stent airways open

- The unique characteristics of CSA-HCSB:
  - provide a natural compensatory mechanism to offset the adverse effects of HF
  - May be most similar to CPAP (see figure)
Summary

- Optimizing HF treatment is agreed upon as effective therapy
- CPAP therapy to treat OSA in HFrEF makes good sense
- PAP therapy to reduce CSA does not have a role in HFrEF
- As for Oxygen we will await the NIH trial
- As for Pacing – a role can not be clearly developed until we understand if there is a benefit to treating central apnea

Thank-You